Cell-Based Therapy for Canavan Disease Using Human iPSC-Derived NPCs and OPCs.

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Public Summary:
Canavan disease (CD) is a fatal brain disease caused by mutation of the aspartoacylase (ASPA) gene, which leads to deficiency in ASPA activity, accumulation of an amino acid substrate N-acetyl-L-aspartate (NAA), demyelination, and vacuolation in the brain. There is neither a cure nor a standard treatment for this disease. In this study, human induced pluripotent stem cell (iPSC)-based cell therapy is developed for CD. A functional ASPA gene is introduced into patient iPSC-derived neural progenitor cells (iNPCs) or oligodendrocyte progenitor cells (iOPCs) via lentiviral transduction or gene editing to generate cell therapy candidates for CD. After transplantation into a CD mouse model, the engrafted cells are able to rescue major pathological features of CD, including deficient ASPA activity, elevated NAA levels, extensive vacuolation, defective myelination, and motor function deficits, in a robust and sustainable manner. Moreover, the transplanted mice exhibit much prolonged survival. These genetically engineered patient iPSC-derived cellular products are promising cell therapies for CD. This study has the potential to bring effective cell therapies, for the first time, to CD children who have no treatment options. The approach established in this study can also benefit many other children who have deadly genetic diseases that have no cure.

Scientific Abstract:
Canavan disease (CD) is a fatal leukodystrophy caused by mutation of the aspartoacylase (ASPA) gene, which leads to deficiency in ASPA activity, accumulation of the substrate N-acetyl-L-aspartate (NAA), demyelination, and spongy degeneration of the brain. There is neither a cure nor a standard treatment for this disease. In this study, human induced pluripotent stem cell (iPSC)-based cell therapy is developed for CD. A functional ASPA gene is introduced into patient iPSC-derived neural progenitor cells (iNPCs) or oligodendrocyte progenitor cells (iOPCs) via lentiviral transduction or TALEN-mediated genetic engineering to generate ASPA iNPC or ASPA iOPC. After stereotactic transplantation into a CD (Nur7) mouse model, the engrafted cells are able to rescue major pathological features of CD, including deficient ASPA activity, elevated NAA levels, extensive vacuolation, defective myelination, and motor function deficits, in a robust and sustainable manner. Moreover, the transplanted mice exhibit much prolonged survival. These genetically engineered patient iPSC-derived cellular products are promising cell therapies for CD. This study has the potential to bring effective cell therapies, for the first time, to Canavan disease children who have no treatment options. The approach established in this study can also benefit many other children who have deadly genetic diseases that have no cure.